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Antineoplastic action of *p*-(3-methyl-1-triazeno)benzoic acid potassium salt, a monomethyl derivative of the antimetastatic compound DM-COOK*

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Summary. The antitumor and antimetastatic effects of *p*-(3-methyl-1-triazeno)benzoic acid potassium salt (MM-COOK) as compared with those of the parent 3,3-dimethyl derivative (DM-COOK) were examined using Lewis lung carcinoma, MCa mammary carcinoma of the CBA mouse and TLX5 lymphoma. Similarly to DM-COOK, MM-COOK reduces metastasis formation and significantly prolongs the survival of mice bearing the Lewis lung carcinoma when given at a daily dose corresponding to one-half that of DM-COOK. Unlike DM-COOK, MM-COOK exhibits significant cytotoxicity to metastatic foci and pronounced inhibition of primary tumor development. MM-COOK also causes cytotoxic effects on TLX5 lymphoma cell growing in the peritoneal cavity, even when used at low doses. The antimetastatic effects observed in mice bearing MCa mammary carcinoma are unrelated to the inhibition of primary tumor growth and are more likely due to the selection of clones endowed with lower metastatic ability. It appears that MM-COOK exhibits the same antineoplastic activity as DM-COOK, but the former does so at a lower daily dose and produces interesting cytotoxic effects other than those reflecting its antimetastatic properties. It thus seems to be a valid alternative to DM-COOK, in view of the possible introduction of newer aryltriazenes into clinical use.

Introduction

A great number of 1-aryl-3,3-dimethyltriazenes, which are structurally related to the clinically used agent 5-imidazole-(3,3-dimethyl-1-triazeno)-4-carboxamide (DTIC), have shown antitumor activity in experimental models of animal tumors [1, 24]. Investigations on the mechanism of their antitumor effect have increased our knowledge of the role of their metabolic transformation and, particularly, of their oxidative *N*-demethylation to the corresponding monomethyl derivatives [2, 27]. No evidence has been provided that indicates a correlation between the antitumor action of dimethyltriazenes and their in vitro conversion to monomethyl derivatives [2, 5, 9, 10, 13].

Indeed, monomethyltriazenes exhibit antitumor properties only in mice bearing TLX5 lymphoma, a poorly predictive experimental system in that the injection of tumor cells and of the drug occurs in the same compartment; when given far from the site of tumor implantation in mice bearing s.c. Lewis lung carcinoma, these compounds are less active [6]. Moreover, in vivo induction and inhibition of hepatic drug metabolism indicates the absence of any role for in vivo production of the corresponding demethylated analogs [23]. On the contrary, monomethyltriazenes appear to be responsible for the chemical xenogenization of murine lymphomas that has been obtained using dimethyltriazenes after either in vitro or in vivo treatments [3, 13, 14]. Among the compounds studied, *p*-(3-methyl-1-triazeno)benzoic acid potassium salt (MM-COOK) seems to be the most promising compound.

In view of the above consideration, the monomethyltriazene MM-COOK seems to be a suitable candidate for the investigation of anticancer activity. The aim of the present work was to investigate the spectrum of antitumor activity of this water-soluble compound in mice bearing two solid metastasizing tumors, Lewis lung carcinoma and the MCa mammary carcinoma of the CBA mouse, and in TLX5 lymphoma. We chose MM-COOK based on the relative lack of information available on water soluble triazenes and because *p*-(3,3-dimethyl-1-triazeno)benzoic acid potassium salt (DM-COOK) shows greater antitumor activity than other dimethyltriazenes [6, 11, 17, 19]. DM-COOK is characterized by its high water solubility, is rather stable under physiological conditions, is much less genotoxic [26] and immunosuppressive than DTIC as determined

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using the skin allograft-rejection test (I. Hrsak, personal communication) and, unlike DTIC, is devoid of hematologic toxicity [20]. DM-COOK has also been shown to produce an inheritable chemical xenogenization of murine lymphomas [3, 13, 14].

MM-COOK mostly retains the favorable chemical properties of DM-COOK, is less immunosuppressive than the latter [14] and is particularly effective in inducing chemical xenogenization of murine lymphomas, even as compared with other dimethyl and monomethyl derivatives [3, 13, 14]. Comparisons of MM-COOK with DM-COOK are presented, when appropriate, in conditions under which the latter has never previously been studied. The effects of drug treatment either on primary tumor growth and pulmonary metastasis formation or on the prolongation of survival were compared with those observed in untreated tumor-bearing controls.

Materials and methods

Synthesis and animal treatment. MM-COOK and DM-COOK were synthesized according to previously reported procedures [4, 13]. The higher dose of MM-COOK used for antitumor testing was extrapolated from plots relating log(dose) vs probit(lethality) according to the method of Litchfield and Wilcoxon [12] and corresponds to the dose that is lethal to 5% of the treated animals ($LD_{0.05}$). The LD_{50} value for daily treatment over 14 consecutive days is 51 mg kg^{-1} day^{-1} (range 40–70.2 mg kg^{-1} day^{-1}), corresponding to one-half that of DM-COOK, obtained using the same animal strain and treatment schedule [23].

These drugs were dissolved in 0.1 *N* $NaHCO_3$ and then given i.p. in volumes of 0.1 ml/10 g body weight. The dose and treatment schedules used for each experiment are indicated in the legend to the appropriate figure. Cyclophosphamide, used at 180 mg/kg at 24 h before tumor implantation for immunosuppression of host recipients, was kindly donated by Schering SpA (Milan, Italy) and was dissolved in 0.9% NaCl.

Tumor lines. The Lewis lung carcinoma line used in the present study was originally obtained from the National Cancer Institute (Bethesda, Md., USA) and was grown in C57BL/6 mice (Charles River; Calco, Como, Italy) after s.c. injection in the axillary region of 50 mm^3 of minced tumor tissue, which was aseptically prepared following its removal from donors that had been similarly inoculated 2 weeks previously. MCa mammary carcinoma, which spontaneously arose in an old, multiparous CBA T6T6 mouse [15], was obtained from the Department of Experimental Biology and Medicine of Rudjer Boskovic Institute (Zagreb, Yugoslavia) and was grown after i.m. inoculation of 50 mm^3 of tumor fragments into the calf of the left hind leg of CBA mice from our conventional breeding colony. TLX5 lymphoma, originally obtained from the Chester Beatty Research Institute (London, England), was maintained and propagated by weekly i.p. transplantations of 10^5 tumor cells into syngeneic CBA mice.

Evaluation of tumor growth. For evaluation of the effects of drug treatment, Lewis lung carcinoma was transplanted into BD2F1 hybrids; syngeneic female and male CBA mice were used for the transplantation of MCa mammary carcinoma and TLX5 lymphoma, respectively. Primary tumor weight and the numbers and weights of lung metastases were determined as previously described in detail [23]. The survival of mice implanted with TLX5 lymphoma recorded. Two routes of tumor inoculation were chosen: i.p. injection of 10^5 cells/mouse in 0.1 ml phosphate-buffered saline (PBS) and i.c. injection of 10^5 cells/mouse in 0.025 ml PBS using a needle for intradermic injections.

Surgical ablation of primary tumor. Surgical experiments were performed in mice bearing i.m. tumors that had been anesthetized with 125 mg/kg i.p. Ketalar [19, 20]; surgical interventions were carried out according to the animal-care guidelines currently in force in Italy.

Results

Differential effects on primary tumor and on lung metastases

In Lewis lung carcinoma, MM-COOK inhibited primary tumor growth and the formation of spontaneous pulmonary metastases in a dose-dependent way (Fig. 1). The reduction in the weight of lung metastases was higher than that in either metastasis number or primary tumor. Conversely, in MCa mammary carcinoma, no reduction in the primary tumor was observed and the reduction in the numbers and weights of metastases was statistically significant only at the higher dose tested, this effect being comparable with that on Lewis lung carcinoma. In this tumor, independently of the daily dose used, DM-COOK significantly reduced

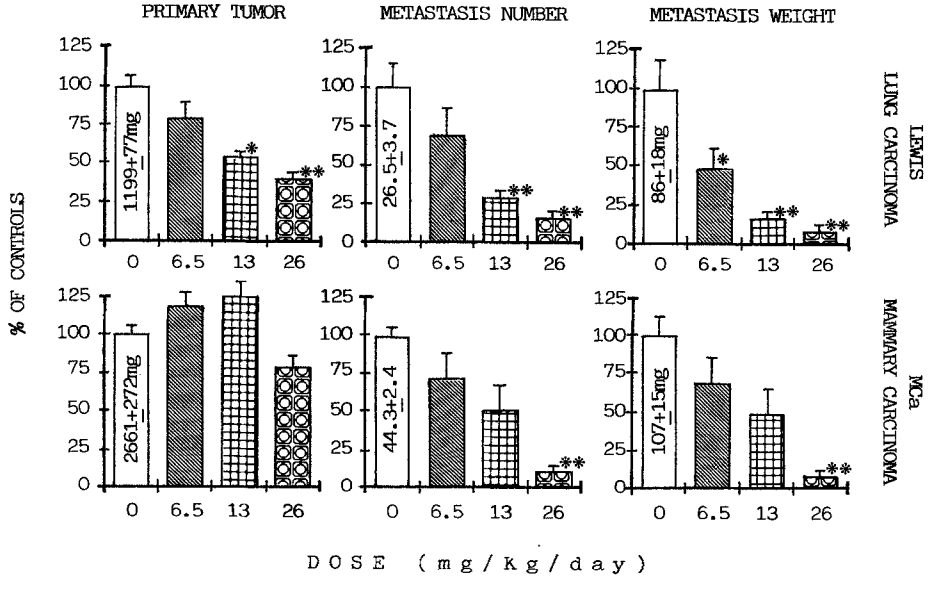

Fig. 1. Effects of MM-COOK on primary tumor growth and on lung metastasis formation in the Lewis lung carcinoma and MCa mammary carcinoma systems. Groups of 10 mice that had been implanted s.c. (i.m. for MCa mammary carcinoma) with the tumor on day 0 were given the test compound i.p. on days 1–14. * $P < 0.05$, ** $P < 0.01$; means statistically different from controls, computerized Student-Newman-Keuls test [25]

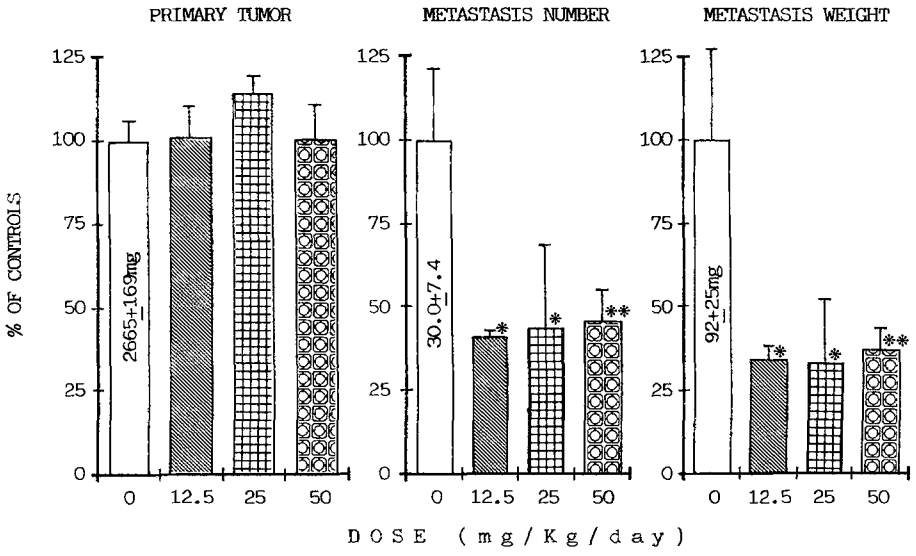

Fig. 2. Effects of DM-COOK on primary tumor growth and on the formation of spontaneous pulmonary metastases in mice bearing MCa mammary carcinoma. Groups of 8 CBA mice that had been implanted i.m. with tumor fragments on day 0 were given the test compound i.p. on days 1–14. * P <0.05, ** P <0.01; means statistically different from controls, computerized Student-Newman-Keuls test [25]

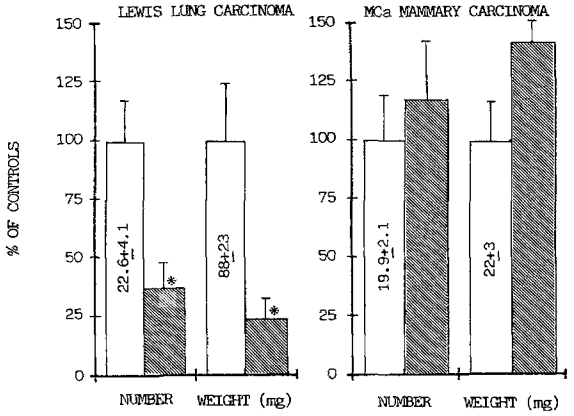

Fig. 3. Effects of MM-COOK on established lung metastases in the Lewis lung carcinoma and MCa mammary carcinoma systems. Groups of 10 mice that had been implanted i.m. with the tumor on day 0 and had undergone surgical ablation of the affected leg on day 12 were given the test compound i.p. on days 13–20 (26 mg kg^{-1} day^{-1}). Animals were killed and their lungs were examined for metastases on day 21. * P <0.05; means statistically different from controls, computerized t-test for grouped data [25]. *White columns*, controls; *hatched columns*, mice treated with MM-COOK

metastasis weight and number to about 30%–40% of control values and but had no effect on primary tumor growth (Fig. 2).

The effects of MM-COOK on established lung metastases, which spontaneously formed in mice with i.m. growing tumors that had been surgically removed before drug treatment, are shown in Fig. 3. MM-COOK significantly reduced the growth of metastases of Lewis lung carcinoma but was completely ineffective against those of MCa mammary carcinoma. Similar results were obtained in mice in which lung colonies had been artificially induced by i.v. inoculation of tumor cells. Indeed, MM-COOK was inactive against metastases resulting from the inoculation of 10^5 cells/mouse but was effective against those produced by the inoculation of lower numbers of cells, giving an average number of lung colonies of 3.7±0.6/animal. In this case, MM-COOK reduced the numbers and weights of lung metastases by 46% and 63%, respectively.

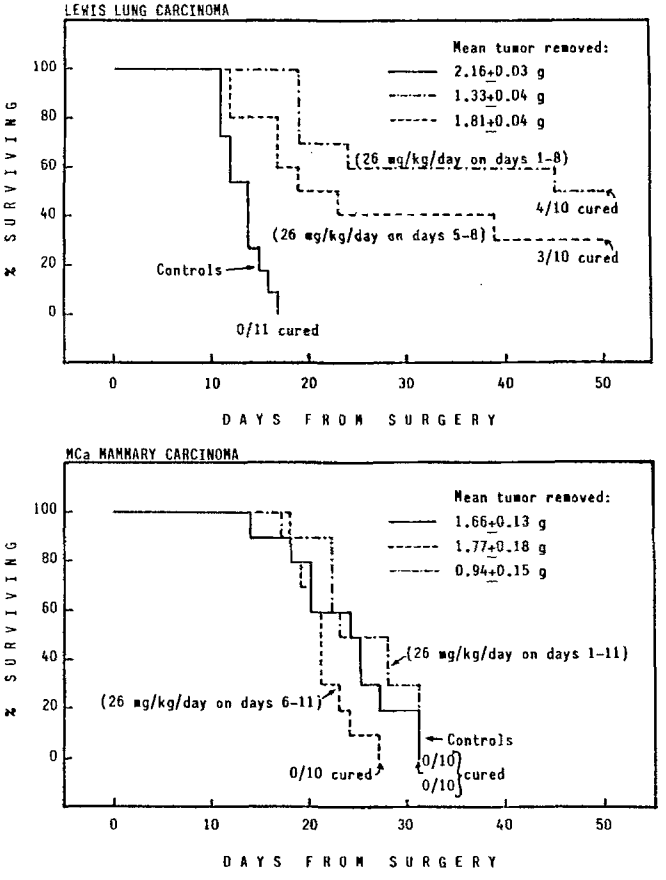

Fig. 4. Effects of MM-COOK on the survival of mice that had undergone surgical ablation of the primary tumor at 24 h after the last drug injection. Groups of 10–11 mice that had been implanted i.m. with the tumor on day 0 were given the test compound i.p. on days 1–8 or 5–8 (Lewis lung carcinoma) or on days 1–11 or 6–11 (MCa mammary carcinoma). Surgical ablation of the primary tumor occurred on day 9 (Lewis lung carcinoma) or on day 12 (MCa mammary carcinoma). Statistical analysis was performed using the computerized Mann-Whitney U-test [25]. Lewis lung carcinoma: MM-COOK on days 1–8 vs controls, P <0.001; MM-COOK on days 5–8 vs controls, P <0.01; MM-COOK on days 1–8 vs MM-COOK on days 5–8, P <0.08

Treatment with MM-COOK given before surgical amputation of the primary tumor in mice bearing, i.m. Lewis lung carcinoma significantly prolonged the animals survival; the drug's efficacy depended on the duration of the treatment (Fig. 4). When given to mice bearing MCa mammary carcinoma, the same treatment was completely uneffective (as was also seen with DM-COOK in separate experiments).

Modification of the metastatic ability of MCa mammary carcinoma

Our examination of the residual metastasizing ability of MCa mammary carcinoma following in vivo treatment with MM-COOK and DM-COOK is reported in Fig. 5. This experiment was designed to study the effects of MM-COOK and DM-COOK on the capacity of tumor cells surviving after treatment to generate tumors and to produce lung metastases over three transplant generations in the absence of further treatments. Data reported in Fig. 5 illustrate the effects on metastasis weight. The effect on metastasis number was of the same magnitude and was omitted for better clarity; primary tumor growth was unaffected as compared with values obtained for untreated controls. The treatment given on days 1–11 to mice bearing MCa mammary carcinoma caused a significant reduction in the weight of metastases found in intact or immunosuppressed CBA mice that had been implanted i.m. with tumor fragments harvested from the treated mice at 24 h after the last drug administration (Fig. 5, transplant generation I). The metastasizing ability of cells treated with MM-COOK also remained reduced for two subsequent transplant generations. The reduction in the metastatic potential of the tumor line that was caused by DM-COOK was less evident at the third transplant generation.

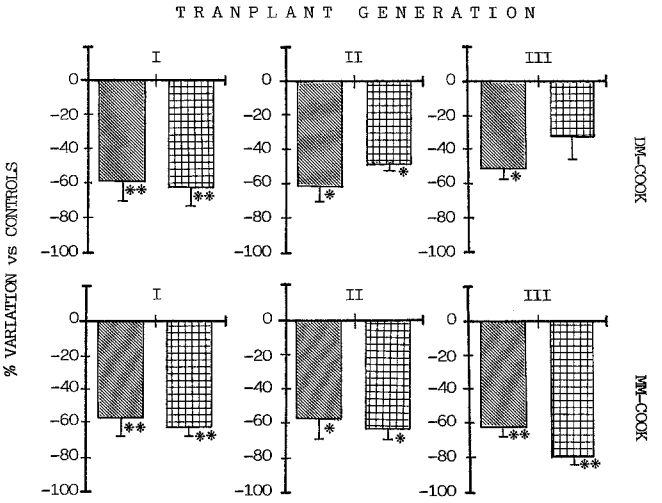

Fig. 5. Effects of DM-COOK and of its monomethyl derivative MM-COOK on the metastasizing ability of MCa mammary carcinoma. Groups of 8 mice, intact (▧) or immunosuppressed (▦) with cyclophosphamide, were implanted i.m. with MCa mammary carcinoma fragments (transplant generation I) obtained from tumor-bearing mice and harvested 24 h after i.p. daily treatment on days 1–11 with DM-COOK (50 mg kg^{-1} day^{-1}) or with MM-COOK (26 mg kg^{-1} day^{-1}). The subsequent transplant generation II (III) was obtained by i.m. transplantation of 50 mm^3 of tumor fragments that had been harvested on day 14 after tumor implantation from mice of transplant generation I (II). Lung metastases were evaluated on day 21 following tumor implantation. Cyclophosphamide (180 mg kg^{-1} day^{-1}) was given i.p. at 24 h prior to tumor inoculation. The actual findings in control groups were: 138±22, 141±28 and 85±12 mg for the 1st, 2nd and 3rd transplant generations, respectively. * P <0.05, ** P <0.01; means statistically different from controls, computerized Student-Newman-Keuls test [25]

Inhibition of TLX5 lymphoma

MM-COOK significantly increased the survival of mice bearing TLX5 lymphoma, showing activity over a broad spectrum of doses ranging from 5 to 80 mg kg^{-1} day^{-1} that were given i.p. on days 1–7 following i.p. implantation of TLX5 lymphoma on day 0. Our comparison of the effects of MM-COOK with those of DM-COOK in mice bearing TLX5 lymphoma is shown in Table 1. Both compounds significantly prolonged the survival of mice bearing TLX5 lymphoma following either i.p. or i.c. tumor inoculation. In particular, MM-COOK exhibited the same activity at both doses tested, the lower being 1/5 that of DM-COOK. The effect on the i.p. growth of TLX5 lymphoma was pronounced; the number of tumor cells recovered at the end of treatment was reduced by 88%, even at the dose of 2.5 mg kg^{-1} day^{-1}, which was considered to be inactive in that it increased the life span by <20%.

Table 1. Comparison of the effects of MM-COOK and DM-COOK on the survival of mice bearing TLX5 lymphoma

Tumor inoculation	Treatment schedule	Survival (days)	
		Mean ±SE	%ILS
10^5 cells/mouse, i.p.	Controls	9.7 ±0.1	–
	DM-COOK 50 mg/kg daily	14.3 ±0.3*	47
	MM-COOK 40 mg/kg daily	16 ±1.0*	65
	MM-COOK 10 mg/kg daily	13 ±0.4*	34
10^5 cells/mouse, i.c.	Controls	8.1 ±0.2	–
	DM-COOK 50 mg/kg daily	12.4 ±1.1*	53
	MM-COOK 40 mg/kg daily	12 ±0.8*	48
	MM-COOK 10 mg/kg daily	12.4 ±0.5*	53

Groups of 5–7 CBA mice (10 controls) that had been inoculated with TLX5 lymphoma cells on day 0 were given the test compounds i.p. on days 1–7
* P <0.05; means statistically different from control values, computerized Student-Newman-Keuls test [25]

Discussion

Our investigation of the antitumor activity of MM-COOK following systemic administration to mice bearing transplantable tumors indicates that this compound is endowed with interesting antitumor properties. In fact, MM-COOK expresses the antimetastatic action of the corresponding dimethyl analog but, unlike DM-COOK, it is also active at the primary site of tumor growth.

In general, it is accepted that monomethyltriazenes are responsible for the cytotoxic activity of the dimethyl compounds [1, 2], whereas their antimetastatic effects have been mainly attributed to mechanisms unrelated to a direct cytotoxicity to tumor cells [7, 22]. The present results indicate that MM-COOK is also responsible for the antimetastatic effects of DM-COOK. Indeed, this conclusion partially contrasts with the previously reported observation that the inhibition rather than the stimulation of in vivo oxidative metabolism augments the cytotoxic and antimetastatic effects of DM-COOK [23]. Furthermore, DM-COOK does not undergo appreciable in vitro *N*-demethylation to the corresponding monomethyl derivative [18, 23].

The low activity of MM-COOK against MCa mammary carcinoma as compared with Lewis lung carcinoma cannot be attributed to the different sites of implantation and growth (i.e. i.m.). Mice that received s.c. implants of MCa mammary carcinoma and were treated with MM-COOK showed the same results: at a dose of 26 mg kg^{-1} day^{-1}, primary tumor growth was only slightly lowered from $1{,}317 \pm 264$ to $1{,}040 \pm 192$ mg, whereas the numbers and weights of lung metastases were statistically significantly reduced by 77% and 81%, respectively. However, it must be emphasized that the activity of DM-COOK against this tumor system was lower than the values observed to date in the other experimental tumors [17, 20, 22].

Interestingly, DM-COOK and, especially MM-COOK significantly modify the metastatic potential of this tumor line. The absence of differences in metastatic expression in intact vs immunosuppressed hosts seems to exclude the role of xenogenizing properties that has previously been observed for these compounds in mouse lymphomas [3, 13]. It seems more likely that a rearrangement of tumor cell heterogeneity occurs after treatment, resulting in the selection of clones endowed with lower metastatic ability. This hypothesis is supported by the antimetastatic action of DM-COOK against the M1087 line, a highly malignant subline of Lewis lung carcinoma [21]. After treatment, the tumor line became less malignant and histologically more similar to the lowly metastasizing line BM21548 [16, 18]. Furthermore, these data are consistent with previous observations indicating the capacity of aryldimethyltriazenes to reduce the metastatic potential of Lewis lung carcinoma [28].

Our comparison of the antitumor activity of MM-COOK and DM-COOK suggests the same effect for the two compounds on the survival of tumor-bearing hosts, independently of the mechanism by which they reduce or control tumor growth. Taken together, these data indicate that MM-COOK can successfully replace DM-COOK, offering the advantage of using a lower dose of xenobiotic and, in some instances, of producing effects that DM-COOK does not provide.

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